

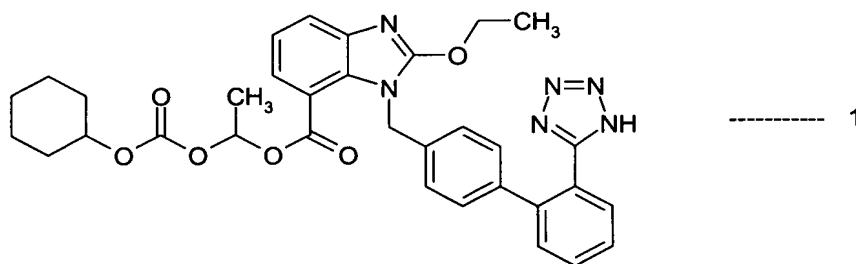
FIELD OF THE INVENTION

5 The present invention relates to two novel crystalline forms and a novel 1,4-dioxane solvate of candesartan cilexetil, to processes for their preparation and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

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Candesartan cilexetil of formula (1):



15 or 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid, 1-[[[(Cyclohexyloxy)carbonyl]oxy]ethyl] ester. Candesartan cilexetil is an antihypertensive agent and its therapeutic uses were disclosed in US 5,196,444. US 5,196,444 also disclosed a crystalline form of candesartan cilexetil (C-type crystalline form). Two crystalline forms of  
20 candesartan cilexetil, form I and form II, are described in Chem. Pharm. Bull. 47(2), 182-186 (1999).

We have discovered a novel 1,4-dioxane solvate of candesartan cilexetil and two novel crystalline forms of candesartan cilexetil. The novel forms have been found to be stable and reproducible.

25 The object of the present invention is to provide a stable novel 1,4-dioxane solvate of candesartan cilexetil and two stable crystalline forms of candesartan cilexetil, processes for preparing these forms and pharmaceutical compositions containing them.

## DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention is to provide a novel 1,4-dioxane solvate of candesartan cilxetil (hereinafter referred to as candesartan cilxetil dioxane solvate). Typically the content of 1,4-dioxane in the solvate is 8.8 to 13.0 % w/w. The candesartan cilxetil dioxane solvate is characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 6.0, 10.7, 16.2, 18.0, 19.7, 20.6, 21.3, 21.7, and 22.3 degrees. Figure 1 shows typical x-ray powder diffraction pattern of candesartan cilxetil dioxane solvate.

Candesartan cilxetil dioxane solvate is prepared by dissolving crystalline form or amorphous form of candesartan cilxetil in 1,4-dioxane and crystallizing at 5°C to 15°C, preferably at 5°C to 10°C.

Another aspect of the present invention is to provide a novel crystalline form of candesartan cilxetil (hereinafter referred to as candesartan cilxetil form III, characterized by an x-ray powder diffraction pattern having peaks at about 6.3, 7.3, 8.1, 8.9, 10.1, 14.6, 15.0, 15.8, and 18.8 degree. Figure 2 shows typical x-ray powder diffraction pattern of candesartan cilxetil form III.

The candesartan cilxetil form III is prepared by dissolving candesartan cilxetil in toluene by heating, cooling the solution slowly to 0°C to 5°C, maintaining at 0°C to 5°C for about 1 hour and separating the crystals formed by filtration. The solvent may be heated to dissolve candesartan cilxetil. Candesartan cilxetil used in the process may be any of the crystalline forms except form III, amorphous form or candesartan cilxetil dioxane solvate.

Another aspect of the present invention is to provide a novel crystalline form of candesartan cilxetil (hereinafter referred to as candesartan cilxetil form IV). The candesartan cilxetil form IV is characterized by an x-ray powder diffraction pattern having peaks at about 6.1, 7.1, 11.6, 11.9, 17.9, 19.8 and 21.2 degree. Figure 3 shows typical x-ray powder diffraction pattern of candesartan cilxetil form IV.

The candesartan cilxetil form IV is prepared by mixing candesartan cilxetil, methyl tert-butyl ether and methanol at 50°C to 55°C and maintaining at 20°C to 25°C for about 10 hours. Candesartan cilxetil used in the process may be any of the crystalline forms except form IV, amorphous form or candesartan cilxetil dioxane solvate.

Candesartan cilexetil used in the above processes may be obtained by the known methods.

In accordance with the present invention, there is provided a pharmaceutical composition comprising crystalline form III or form IV of  
5 candesartan cilexetil and a pharmaceutically acceptable carrier.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction pattern of candesartan cilexetil dioxane solvate.

10 Figure 2 is a x-ray powder diffraction pattern of candesartan cilexetil form III.

Figure 3 is a x-ray powder diffraction pattern of candesartan cilexetil form IV.

x-Ray powder diffraction spectrum was measured on a Siemens D5000 x-ray powder diffractometer having a copper-K $\alpha$  radiation.

15 The following examples further illustrate the invention.

#### Example 1

Candesartan cilexetil C-type crystalline form (5 gm, obtained by a process described in US 5,196,444) is dissolved in 1,4-dioxane (50 ml) at 25°C.  
20 The solution is cooled to 5°C and maintained for 4 hours at about 5°C. The separated solid is filtered to yield 3 gm candesartan cilexetil dioxane solvate.

#### Example 2

Candesartan cilexetil C-type crystalline form (5 gm) is added to toluene  
25 (25 ml) and heated to reflux. The contents are maintained under reflux for 15 minutes and then cooled slowly to 0°C in 1 hour and maintained at 0°C to 5°C for 1 hour. The separated crystals are collected by filtration to give 3.5 gm candesartan cilexetil form III.

#### Example 3

30 Example 1 is repeated using candesartan cilexetil form III instead of candesartan cilexetil C-type crystalline form to give Candesartan cilexetil dioxane solvate.

#### Example 4

The mixture of candesartan cilexetil C-type crystalline form (5 gm), methyl tert-butyl ether (50 ml) is heated to 55°C, methanol (17 ml) is added to the mixture at 55°C and maintained at about this temperature for 1 hour. The contents are cooled to 25°C and maintained at about 25°C for 13 hours. The  
5 separated solid is collected by filtration to give 3 gm candesartan cilexetil form IV.

#### Example 5

Example 2 is repeated using candesartan cilexetil form IV instead of  
10 candesartan cilexetil C-type crystalline form to give Candesartan cilexetil form III.

#### Example 6

Example 4 is repeated using candesartan cilexetil dioxane solvate instead of candesartan cilexetil C-type crystalline form to give Candesartan  
15 cilexetil form IV.

We claim:

1. A candesartan cilexetil 1,4-dioxane solvate.
2. A candesartan cilexetil 1,4-dioxane solvate of claim 1, wherein the content of 1,4-dioxane is 8.8 to 13.0 % w/w.
- 5 3. A candesartan cilexetil 1,4-dioxane solvate of claim 1, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 6.0, 10.7, 16.2, 18.0, 19.7, 20.6, 21.3, 21.7, and 22.3 degrees.
4. Candesartan cilexetil 1,4-dioxane solvate of claim 3, further characterized by an x-ray powder diffraction pattern as in figure 1.
- 10 5. A process for the preparation of candesartan cilexetil 1,4-dioxane solvate of claim 1, which comprises:
  - a) dissolving candesartan cilexetil in 1,4-dioxane; and
  - b) crystallizing candesartan cilexetil as 1,4-dioxane solvate from the solution at 5°C to 15°C.
- 15 6. A process according to claim 5, wherein candesartan cilexetil used is a crystalline or amorphous form of candesartan cilexetil.
7. A process according to claim 6, wherein the crystalline form of candesartan cilexetil is candesartan cilexetil form III.
8. A crystalline candesartan cilexetil form III, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 6.3, 7.3, 8.1, 8.9, 10.1, 14.6, 15.0, 15.8, and 18.8 degrees.
- 20 9. Candesartan cilexetil form III of claim 8, further characterized by an x-ray powder diffraction pattern as in figure 2.
10. A process for the preparation of candesartan cilexetil form III of claim 8,
  - 25 which comprises:
    - a) mixing candesartan cilexetil with toluene;
    - b) heating to obtain clear solution;
    - c) cooling slowly to 0°C to 5°C in about 1 hour;
    - d) maintaining at 0°C to 5°C for about 1 hour; and
    - 30 e) filtering the separated solid.
  11. A process according to claim 10, wherein candesartan cilexetil used is candesartan cilexetil as 1,4-dioxane solvate of claim 1.

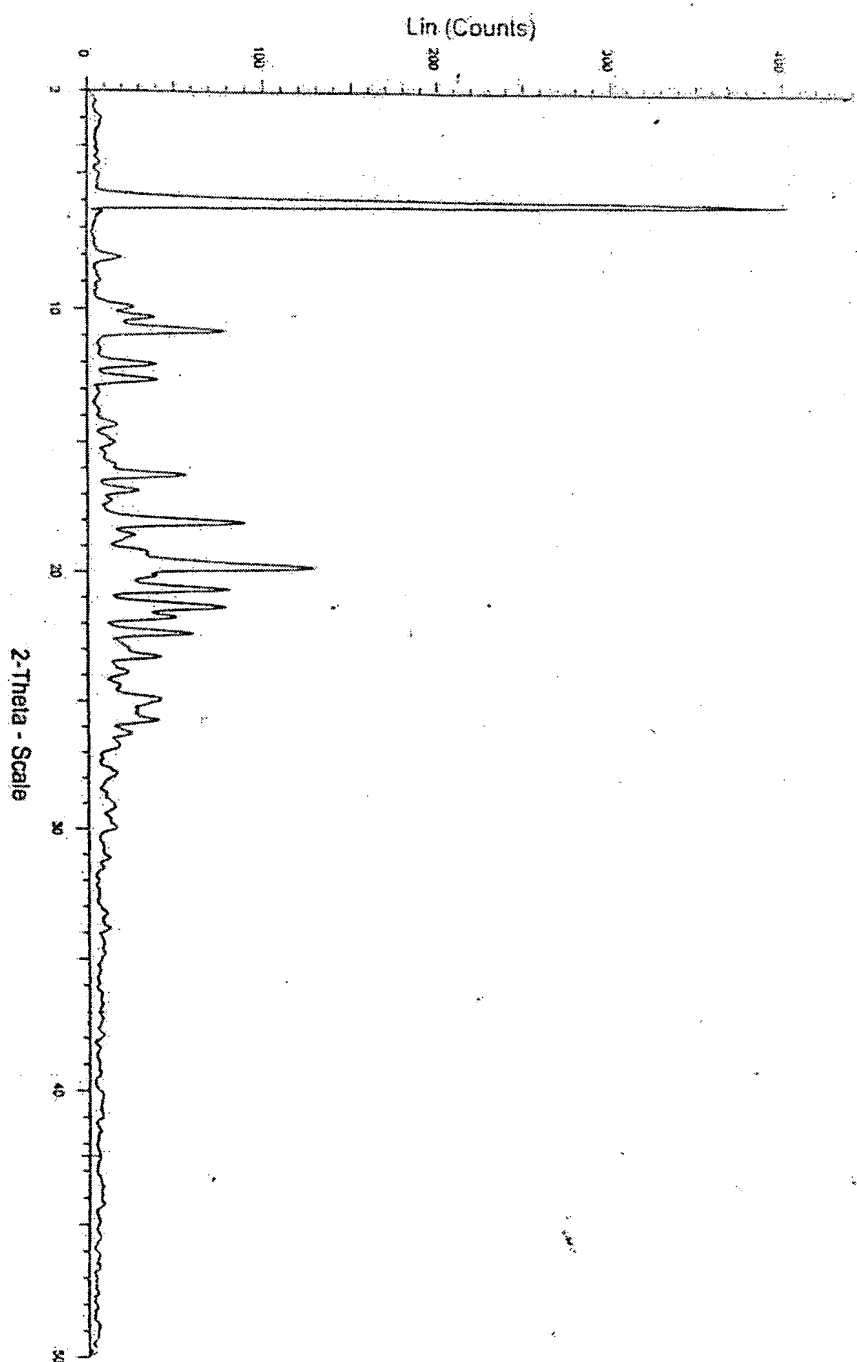
12. A crystalline candesartan cilexetil form IV, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 6.1, 7.1, 11.6, 11.9, 17.9, 19.8 and 21.2 degrees.
13. Candesaratan cilexetil form IV of claim 12, further characterized by an x-ray powder diffraction pattern as in figure 3.
14. A process for the preparation of candesartan cilexetil form IV of claim 12, which comprises:
- heating the mixture of candesartan cilexetil, methyl tert-butyl ether and methanol to  $50^{\circ}\text{C}$  to  $55^{\circ}\text{C}$ ;
  - cooling to  $20^{\circ}\text{C}$  to  $25^{\circ}\text{C}$ ;
  - maintaining at  $20^{\circ}\text{C}$  to  $25^{\circ}\text{C}$  for about 10 hours; and
  - separated crystals are collected by filtration.
15. A process according to claim 14, wherein candesartan cilexetil used is a crystalline or amorphous or dioxane solvated form of candesartan cilexetil.
16. A process according to claim 15, wherein candesartan cilexetil used is candesartan cilexetil 1,4-dioxane solvate of claim 1.
17. A process according to claim 15, wherein candesartan cilexetil used is candesartan cilexetil form III of claim 8.
18. A pharmaceutical composition comprising candesartan cilexetil form III of claim 8 or candesartan cilexetil form IV of claim 12 and a pharmaceutically acceptable carrier.
19. A pharmaceutical composition of claim 18, wherein candesartan cilexetil form III is used.
20. A pharmaceutical composition of claim 18, wherein candesartan cilexetil form IV is used.

**Abstract:**

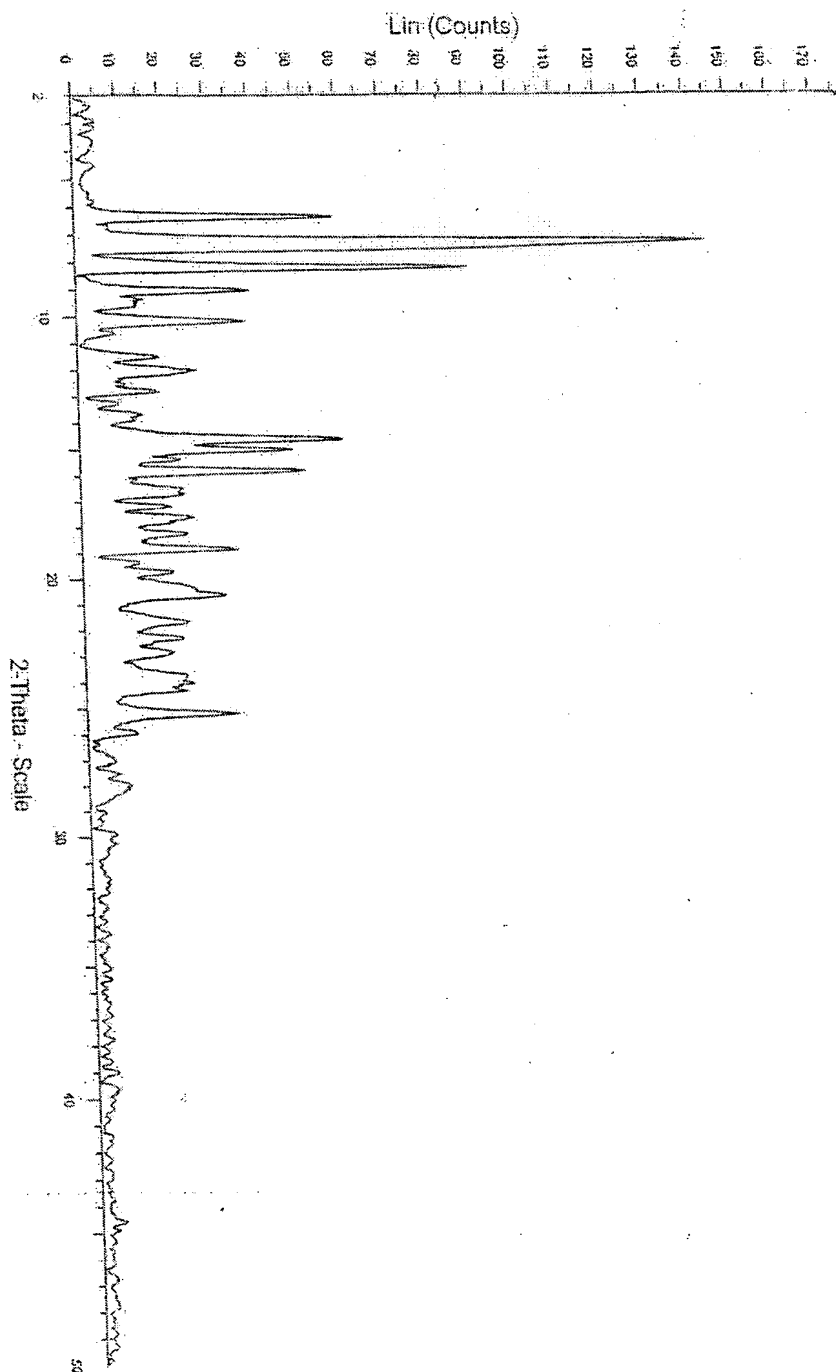
The present invention relates to two novel crystalline forms and a novel 1,4-dioxane solvate of candesartan cilexetil, to processes for their preparation and to pharmaceutical compositions containing them.

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fig. 1/3



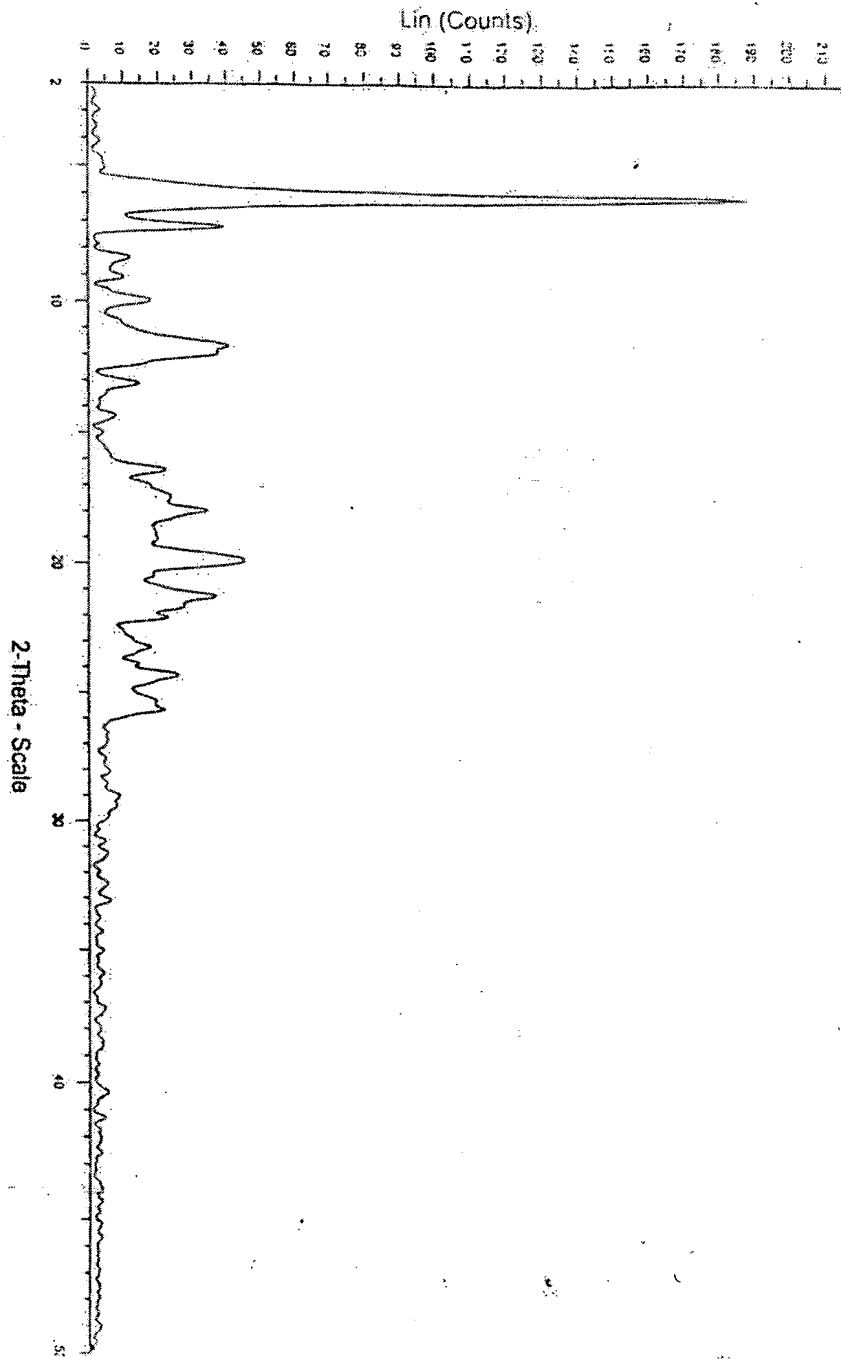
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fig. 3/3



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